Category

Best Startup

Product/Solution Name

PT-112

Date of Approval

N/A

Indications

In development for:
- Prostate Cancer
- Lung Cancer
- Thymoma and Thymic Carcinoma
- Multiple Myeloma

Therapeutic Categories

Anticancer immunogenic small molecule

Attached Files:
- Promontory Therapeutics_Prix Galien USA Submission Slides_Intro.pdf

Background information and need for solution/product

While cancer immunotherapy has achieved remarkable progress, there are limitations to therapeutics directed at T-cell checkpoints. For the majority of patients other options are needed. This is particularly acute in diseases exhibiting limited immune cell tumor infiltration, or when such cells are anergic ("immune cold"), such as metastatic prostate cancer. We are at the forefront of small molecule therapeutics that can modulate immune regulatory pathways and trigger immune activation. In 2023, in conjunction with the National Cancer Institute, the company published the first data demonstrating immune activation with PT-112 in cancer patients.

The company's lead candidate, PT-112, is a novel small molecule inhibitor of ribosomal biogenesis, leading to immunogenic cancer cell death (ICD). This novel mechanism of action creates the integrated stress response, whereby cancer cells die in a fashion that releases immune signaling molecules. This contrasts with apoptosis, which is generally tolerated by the immune system. ICD may bridge activation of both the adaptive and innate immune responses. The data presented by NCI suggest that PT-112 achieves this.

Promontory Therapeutics Inc. is a private New York City-based, clinical-stage biotech company specializing in small molecule immunotherapy, with the goal of redefining cancer treatments by harnessing the innate power of patients' immune systems. The company was founded upon the in-licensing of a family of compounds synthesized by Rathindra Bose, PhD at Ohio University. We have shown significant evidence of immune activation in patients with late-stage prostate, lung, and thymic cancers.

Our outstanding internal team of 22 staff is augmented by a diverse array of professionals on our board of directors and scientific advisory board. These individuals comprise world-class industry experts, leading researchers, eminent medical oncologists, and biomarker specialists.

We collaborate with universities, pharmaceutical firms, and specialty research companies across the US, Europe, and Asia. Among these partnerships, we work with the National Cancer Institute (NCI), including James Gulley, MD, co-Director of the Center for Immuno-Oncology. NCI is leading our Phase 2 study in thymic cancers along with translational research and immuno-profiling. Under regulatory allowance in France, this year we have expanded our prostate cancer Phase 2 study into French cancer research institutes, led by Karim Fizazi, MD, PhD at the Gustave Roussy in Paris and are exploring working with the Paris Saclay Cancer Cluster to broaden our research initiatives. Our Scientific Advisory Board is led by Daniel Von Hoff, MD, former President of the AACR, and includes Howard Scher, MD, of Memorial Sloan Kettering Cancer Center, who is founder and chair of the Prostate Cancer Working Group, and Lorenzo Galluzzi, PhD, of Weill Cornell Medical College, a pioneer in the ICD research field.

As an independently funded company, Promontory Therapeutics has steered PT-112 through preclinical to Phase 2 and expanded our clinical programs beyond the US into Switzerland and, most recently, France. As we submit our application for the Prix Galien USA Award, we have a clear perspective on the field, yet recognize the steepness of the mountain we still have to climb, a challenge reflected in our name "Promontory."

Attached Files:

- Promontory Therapeutics_Prix Galien USA Submission Slides_Background.pdf

History of the development of the solution/product

Promontory Therapeutics has completed three Phase I trials, received two FDA Orphan Drug designations for PT-112 in relapsed/refractory multiple myeloma (RRMM) and thymic epithelial tumors (TETs), and initiated three Phase 2 programs with PT-112. We have also characterized PT-112's novel mechanism and immune effects, including in peer-reviewed publications. We in-licensed PT-112 at discovery stage, and we currently hold a global IP portfolio comprising composition of matter, manufacturing, and methods of use, on this promising clinical asset.

Our Phase I first-in-human study of PT-112 in advanced solid tumors demonstrated safety and activity in heavily pretreated patients who had exhausted available therapies. Responses included hallmarks of immune engagement – namely durable responses, or responses that deepened following treatment discontinuation – the first clinical clues of PT-112's immunogenicity. We later conducted a Phase Ib study in combination with anti-PD-L1 inhibition in collaboration with Pfizer and Merck KGaA, demonstrating efficacy and feasibility of this combination among both prostate and lung cancer patients. In addition to solid tumors, PT-112 was active in a Phase I study in RRMM, which was launched after observing robust efficacy in highly predictive, genetically engineered mouse models.

Our early clinical findings and PT-112's immunogenicity led to prioritizing three indications for Phase 2 development in the US and Europe: metastatic castration-resistant prostate cancer (mCRPC); TETs under NCI sponsorship; and in non-small cell lung cancer (NSCLC) in combination with PD-L1 immune checkpoint inhibition. At the 2022 European Society of Medical Oncology (ESMO) Immuno-Oncology Congress, we reported meaningful efficacy in lung cancer patients who had progressed on prior

immuno/chemotherapy, in a study led by Solange Peters, MD, PhD, prior President of ESMO. Moreover, PT-112-driven immune activation was recently published by the NCI, contributing to our human proof-of-mechanism through correlative research including biomarker, immune, and pharmacodynamic profiling.

In parallel to clinical development, we have also achieved a robust, reproducible pre-commercial drug substance and drug product, with manufacturing processes in the US and Europe. This effort makes the program nearly NDA-ready under requirements for chemistry, manufacturing, and controls (CMC).

Despite our company's small size, we have a prominent public presence, having published several peer-reviewed manuscripts, presented at more than 15 conferences, and contributed as panelists/presenters in industry meetings. We won the best poster among all developmental therapeutics at the 2018 ESMO Annual Congress and were selected for an oral presentation in the Investigational Immunotherapy category at ESMO 2020. We also received the "Cancer Immunology Solution of the Year" award from the 2022 BioTech Breakthrough Awards program, among more than 1350 nominations from over 12 different countries.

With PT-112's favorable safety, clinical benefit, and strong preclinical and correlative data, we will continue to generate evidence of drug activity and immunogenicity to achieve our mission of improving treatment outcomes. Our Company is poised to lead the emerging field of small molecule immuno-oncology.

Attached Files:

- Promontory Therapeutics_2020_ASH Poster Presentation.pdf
- Promontory Therapeutics_2020_ESMO_Poster Presentation.pdf
- Promontory Therapeutics_2022_ESMO IO_Poster.pdf
- Promontory Therapeutics_2022_Karp et al_eClinicalMedicine.pdf
- Promontory Therapeutics_2023_ASCO GU_Poster.pdf
- Promontory Therapeutics_Prix Galien USA Submission Slides_Development.pdf
- Promontory Therapeutics_2020_ASCO GU_Poster.pdf
- Promontory Therapeutics_2018_ESMO_Poster.pdf
- Promontory Therapeutics_2023_ASCO.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

PT-112 is a robust immunogenic cell death (ICD)-inducing anticancer agent at the leading edge of small molecule immunotherapy. With demonstrated clinical activity and tolerability, its novel mechanism of action represents a cornerstone to solving unmet needs in immuno-oncology. Distinct from biologics, PT-112 provides a viable solution for challenges with T-cell-directed approaches, including intracellular targeting. PT-112 is well tolerated, with safety data to date lacking immune-related adverse events typically associated with immune checkpoint inhibitors. Together, these properties make this an appealing approach for cancer patients.

Central to PT-112's mechanism is inhibition of ribosomal biogenesis (RiBi) in cancer cells, inducing downstream organelle stress culminating in ICD and anticancer immunity. Due to cancer cells' heightened reliance on RiBi for aberrant proliferation, they are extremely sensitive to PT-112-induced RiBi inhibition, meaning cell death is selective to cancer cells. Mitochondria and endoplasmic

reticulum stress triggers the integrated stress response with release of immune signaling molecules called damage-associated molecular patterns (DAMPs). These ICD hallmarks facilitate anticancer immune activation, binding to dendritic and natural killer cell receptors, allowing for engagement of both the innate and adaptive immune systems. This is the cornerstone of PT-112's ability to elicit durable responses in patients.

Many non-small cell lung cancer (NSCLC) patients do not respond to immune checkpoint inhibitors (ICIs). In addition, following prior immune checkpoint inhibition and chemotherapy, lung cancer patients have no effective and durable therapeutic options available. In the case of metastatic castration-resistant prostate cancer (mCRPC) immune checkpoint inhibitors have failed to reach regulatory approval. PT-112 overcomes such challenges via its differentiated mechanism and related immune activation. We believe this may explain the durable therapeutic benefits observed in several heavily pretreated patients who fit the patient profile described above.

Due to its preferential bio-distribution to bone, lung and liver, PT-112 has shown encouraging results in tumors with multi-site metastatic burden, including visceral and bone disease, such as prostate cancer, lung cancer and multiple myeloma.

Another attractive and innovative feature of PT-112 is its utility in settings where other immune-related agents like ICIs are not feasible due to autoimmune complications, such as thymic epithelial cancers (TETs). With no FDA/EMA approved drug for this rare disease, PT-112 offers TET patients a safe and effective immune-activating treatment option in our ongoing, NCI-sponsored Phase 2 study. An abstract submitted by the NCI was accepted for oral presentation at the International Thymic Malignancy Interest Group (ITMIG) annual meeting in October.

PT-112-induced anticancer immune response, particularly in immunologically cold tumors, highlights the untapped potential of small molecule cancer immunotherapy, the mission-driven focus of Promontory Therapeutics. Based on Phase I/II date, we believe that PT-112's distinct mechanism, combined with clinical benefit and safety, allows for improved patient outcomes across multiple cancer types, beginning with mCRPC, TETs, and eventually in NSCLC, RRMM and other indications. Promontory pushes the frontiers of scientific exploration for small molecule immuno-oncology and presents innovative strategies that address pressing unmet needs. Importantly, these can be deployed globally, including areas where other technologies like cell-based and biologic therapies are not readily accessible.

Attached Files:

- Promontory Therapeutics_2017_ASH_Poster.pdf
- Promontory Therapeutics_2020_Yamazaki et al_OncoImmunology.pdf
- Promontory Therapeutics_2022_SITC_Poster.pdf
- Promontory Therapeutics_Prix Galien USA Submission Slides_Innovation.pdf
- Promontory Therapeutics_2022_AACR_Poster.pdf
- Promontory Therapeutics_2022_SolerAgesta et al_Cancers.pdf
- Promontory Therapeutics_2015_CorteRodrguez et al_Biochemical Pharmacology.pdf
- Promontory Therapeutics_2016_ENA_Poster.pdf
- Promontory Therapeutics_2015_ENA_Poster.pdf

Please provide appropriate references (ie Pubmed links)

Select Manuscripts

Soler-Agesta et al., PT-112 induces mitochondrial stress and immunogenic cell death, targeting tumor cells with mitochondrial deficiencies (2022) (https://pubmed.ncbi.nlm.nih.gov/36010843/)

Karp et al., Phase I study of PT-112, a novel pyrophosphate-platinum immunogenic cell death inducer, in advanced solid tumours (2022) (https://pubmed.ncbi.nlm.nih.gov/35747193/)

Yamazaki et al., PT-112 induces immunogenic cell death and synergizes with immune checkpoint blockers in mouse tumor models (2020) (https://pubmed.ncbi.nlm.nih.gov/32117585/)

Corte-Rodríguez et al., Quantitative evaluation of cellular uptake, DNA incorporation and adduct formation in cisplatin sensitive and resistant cell lines: Comparison of different Pt-containing drugs (2015) (https://pubmed.ncbi.nlm.nih.gov/26352094/)

Select Abstracts

McAdams et al., Preliminary efficacy, safety, and immunomodulatory effects of PT-112 from a phase 2 proof of concept study in patients (pts) with thymic epithelial tumors (TETs) (2023) - ASCO (https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.e20647)

Bryce et al., A phase 2 study of immunogenic cell death inducer PT-112 in patients with metastatic castration-resistant prostate cancer (2023) - ASCO GU (https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.6_suppl.TPS292)

Yamazaki et al., Immunologically relevant effects of PT-112 on cancer cell mitochondria (2022) - SITC (https://jitc.bmj.com/content/10/Suppl_2/A1162)

Imbimbo et al., A phase IIa study of the novel immunogenic cell death (ICD) inducer PT-112 plus avelumab (“PAVE”) in advanced non-small cell lung cancer (NSCLC) patients (pts) (2022) - ESMO IO (https://doi.org/10.1016/j.iotech.2022.100237)

Soler-Agesta et al., PT-112 induces potent mitochondrial stress and immunogenic cell death in human prostate cancer cell lines (2022) - AACR (https://doi.org/10.1158/1538-7445.AM2022-1115)

Bryce et al., A phase 1b study of novel immunogenic cell death inducer PT-112 plus PD-L1 inhibitor avelumab in metastatic castrate-resistant prostate cancer (mCRPC) patients (2021) - ASCO (https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e17025)

Kourelis et al., A Phase I dose escalation study of PT-112 in patients with relapsed or refractory multiple myeloma (2020) - ASH (https://doi.org/10.1182/blood-2020-134916)

Bryce et al., PT-112 in advanced metastatic castrate-resistant prostate cancer (mCRPC), as monotherapy or in combination with PD-L1 inhibitor avelumab: Findings from two phase I studies (2020) - ASCO GU (https://ascopubs.org/doi/10.1200/JCO.2020.38.6_suppl.83)

Karp et al., Phase Ib dose escalation study of novel immunogenic cell death (ICD) inducer PT-112 plus PD-L1 inhibitor avelumab in solid tumors (2020) - ESMO (https://www.annalsofoncology.org/article/S0923-7534(20)41142-1/fulltext)

Karp et al., A well-tolerated novel immunogenic cell death (ICD) inducer with activity in advanced solid tumors (2018) - ESMO (https://www.annalsofoncology.org/article/S0923-7534(19)48903-5/fulltext)

Ames et al., Translational research of PT-112, a clinical agent in advanced phase I development: evident bone tropism, synergy in vitro with bortezomib and lenalidomide, and potent efficacy in the Vk*MYC mouse model of multiple myeloma (2017) - ASH (http://www.bloodjournal.org/content/130/Suppl_1/1797)

Ames et al., Findings across pre-clinical models in the development of PT-112, a novel investigational platinum-pyrophosphate anti-cancer agent (2016) - AACR-NCI-EORTC (http://www.ejcancer.com/article/S0959-8049(16)33054-4/abstract)

Wang et al., Characterization of molecular targets of the novel platinum agent PT-112 in human colon cancer cells (2015) - AACR-NCI-EORTC (https://doi.org/10.1158/1535-7163.TARG-15-C32)